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# Tumour growth rates and RECIST criteria in early drug development

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ABSTRACT

*Purpose:* The evaluation of treatment efficacy with RECIST criteria does not take into account tumour growth dynamics. We notably investigated the impact of the pre-treatment tumour growth rate (GR) on the evaluation of treatment response.

*Patients and methods:* Seventy-six patients included in phase I clinical trials had scanographic evaluations before and after starting an experimental treatment. The GR was calculated for the pre-treatment period and for the experimental period (i.e. during the new treatment). Tumour response was evaluated per protocol at week 12 and at week 24 of the experimental period according to RECIST criteria. We studied the relation between pre-treatment and experimental GRs and RECIST tumour response.

*Results:* On average the tumour GR was decreased by 40% during the experimental period; compared to the pretreatment period ($p = 0.03$). An increased growth rate (acceleration of GR during experimental treatment compared to pretreatment) was observed in 20 (38%) of the 53 patients considered as non-progressive at week 12 according to RECIST. Conversely a decreased GR was observed in 12 out of 23 (53%) patients classified as progressive according to RECIST. The variation in the GR between the pre-treatment and experimental period was not significantly correlated with response evaluated according to RECIST at week 12 or at week 24 ($p = 0.45$ and 0.44, respectively).

*Conclusions:* RECIST evaluation of tumour response depends on the natural history of the tumours and poorly measures the impact of treatment on the kinetics of tumour growth. Integrating pre-treatment GR evaluations could substantially improve the assessment of treatment efficacy in drug development.



## 1. Introduction

RECIST (Response Evaluation Criteria in Solid Tumours) is the standard guideline for assessing tumour response for most clinical trials in oncology.[1] Response evaluation is based on a comparison between the measurement of several targets just before the start of the new treatment and measurement of the

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same targets at specific times during the course of the new treatment.

RECIST evaluations do not take into account tumour growth characteristics and notably its pre-treatment component. Thus, the categorisation of tumour response according to RECIST criteria may not reflect the ability of an anticancer treatment to modify tumour growth by inducing some degree of tumour regression or by slowing down tumour growth.

We evaluated the possible influence of pre-treatment tumour growth characteristics on treatment evaluation according to RECIST and investigated the feasibility and impact of using pre-treatment evaluations of the tumour growth rate to improve the evaluation of treatment efficacy.

## 2. Material and methods

All patients included in phase I trials at Institut de cancérologie Gustave Roussy (IGR) between January 2005 and July 2008, who had at least two CT-scan evaluations before the start of an experimental treatment, a baseline CT-scan ($D_0$), and at least one evaluation after $D_0$ were eligible. Seventy-six of 317 patients included in our phase I trials during that timeframe met these criteria. The remaining 241 patients were not included because they had fewer than two pre-treatment CT-scans available: 53 patients had no CT-scans before $D_0$ because the phase I trial was the first line of treatment, the 188 other patients had only one of the two required pre-experimental treatment CT-scans because: previous treatment were performed outside our Institution and/or evaluation(s) could not be retrieved; CT-scans were less than 4 week-apart or patients presented haematological tumours not evaluated by RECIST. Patients received no treatment during a wash-out period of at least 4 weeks before starting the experimental treatment.

All patients signed an informed consent form agreeing to participate in the phase I trial. Patients provided freely all 'available' CT-scans that had been performed during the previous treatment lines.

### 2.1. CT-scan evaluations

During the experimental treatment, CT-scan evaluations were performed as required by the phase I protocols. The minimum interval of time between two successive evaluations while on therapy was 3 weeks. Two senior radiologists (CD, FB) selected the target lesions on the baseline CT-scan. These two radiologists monitored the target lesions throughout the experimental treatment period. A medical oncologist (CGR) and a junior radiologist (IM) tracked back and measured the target lesions on pre-treatment CT-scans (the same target lesions as those monitored during the experimental treatment period). All measurements were supervised by at least one senior radiologist (CD, FB or both). Tumour response was assessed according to the variation in the sum of the diameters of the target lesions. Progression corresponded to an increase of more than 20% in the sum of the diameters and/or the detection of new lesions. Stable disease was defined as no new lesion, and an increase equal to or less than 20% of the sum of lesion diameters. A response was defined as no new lesion, and a decrease equal to or greater than 30% of the sum of lesion diameters.

### 2.2. Evaluation of tumour growth dynamics

Tumour size ($D$) was defined as the sum of the largest diameters of 1–10 lesions. Tumour volume ($V$) was approximated by $V = \pi D^3/2$.

The tumour growth rate (GR) was defined as an increase in tumour volume during 1 month. Assuming exponential growth, the GR is constant and equal to

$$GR = dV/dt = \log_{10}(V_t/V_0)/dt$$

where $dV$ is the variation in tumour volume, $V_0$ and $V_t$ the tumour volume at time 0 and at time $t$, respectively, and $dt$ the time in months elapsed between time 0 and time $t$.

We considered two time periods for each patient: (a) the pre-treatment period, from the last tumour evaluation obtained before $D_0$ and $D_0$ and (b) the experimental period, from $D_0$ to the last available tumour evaluation before the end of the experimental treatment. GR variations were estimated for each patient as the difference between the GR measured during the experimental period minus the pretreatment GR.

### 2.3. Statistical analyses

The differences between GR distributions according to tumour progression at 12 weeks and at 24 weeks were tested with Kruskal–Wallis tests. The correlation between GR variation and RECIST response was tested with spearman rank correlation test. The GR variations were compared using non-parametric tests.

## 3. Results

Patient characteristics are summarised in Table 1. The median number of previous tumour treatment lines was 3. A total of 370 evaluations were performed: 76 before $D_0$, 76 at $D_0$ and 218 after the initiation of the experimental treatment. The median number of lesions monitored per patient was 3. At week 12, 23 patients were classified in progression, and 54 at week 24.

### 3.1. RECIST evaluation of tumour response is correlated to pretreatment growth rate

During the pre-treatment period the growth rate was significantly higher in patients exhibiting progression at week 12 (median 0.16 for non-responders versus 0.07 for patients with stable disease; $p = 0.001$) and at week 24 (median 0.09 versus 0.04; $p = 0.008$, Table 2).

### 3.2. RECIST evaluation of tumour response is correlated to experimental growth rate

The growth rate measured during the experimental period was significantly higher in patients exhibiting progression at week 12 (median 0.14 versus 0.03 for other patients, $p < 10^{-4}$) and at week 24 (median 0.08 versus 0.01; p = 0.0001, Table 2).

**Table 1 – Patient demographics and trial treatment.**

| | N patients (%) |
|---|---|
| Female gender | 30 (39.5) |
| *Primary tumour site* | |
| Non-small cell lung cancer | 21 (27.6) |
| Sarcoma | 12 (15.8) |
| Gastrointestinal site other than colorectal | 8 (10.5) |
| Head and Neck | 6 (7.9) |
| Gynaecologic | 6 (7.9) |
| Breast | 5 (6.6) |
| Colorectal | 5 (6.6) |
| Mesothelioma | 3 (3.9) |
| Melanoma | 2 (2.6) |
| Genital-urinary | 1 (1.3) |
| Other | 7 (9.2) |
| *Number of evaluated lesions* | |
| One lesion | 8 (10.5) |
| Two lesions | 15 (19.7) |
| Three lesions | 16 (21.1) |
| Four lesions | 15 (19.7) |
| Five lesions and more | 22 (28.9) |
| *Reason for finishing phase I trial (1 patient still under treatment)* | |
| disease progression | 57 (76.0) |
| Toxicity | 14 (18.7) |
| Patient's decision | 4 (5.3) |

### 3.3. *Tumour growth rate is decreased after the start of experimental treatment*

Overall, the growth rate was significantly smaller during the experimental period compared to the pre-treatment period (0.08 for pre-treatment period versus 0.05 for the experimental period; median decrease −0.02; $p = 0.034$).

### 3.4. *The decrease in GR during the experimental period is less marked for patients classified in progression than for other patients*

The growth rate decreased from 0.16 to 0.14 (median GR decrease = 0.0; $p = 0.99$) between the pretreatment and the experimental period for patients in progression at week 12 and from 0.07 to 0.03 (median GR decrease −0.03; $p = 0.003$) for patients not in progression at week 12. However, the GR decrease observed in progressive patients was not significantly different from the GR decrease observed in non-progressive patients (median 0.0 versus −0.03; $p = 0.15$). Similar results were obtained when groups of patients were defined according to response at week 24 (median GR decrease for patients in progression: −0.02; and −0.03 for patients not in progression; $p = 0.26$).

### 3.5. *The RECIST classification is poorly correlated to the variation of GR*

The variation of tumour growth rate was not significantly correlated with the RECIST response at week 12 nor the RECIST response at week 24 ($p = 0.44$ and 0.45, respectively, Table 3). Among the 53 patients not in progression at week 12, 20 presented an increased GR during the experimental period as compared to the pre-treatment period. Conversely 12 out of the 23 patients classified 'in progression' at week 12 had a decreased GR during experimental period compared to the late

**Table 2 – Median (inter-quartile range) of pre-treatment and experimental growth rate according to RECIST status at week 12.**

| | Number of patients | Pretreatment period | Experimental period | *p*-Value |
|---|---|---|---|---|
| All patients | | 0.08 (0.04–0.15) | 0.05 (0.01–0.11) | 0.034 |
| *RECIST status at week 12* | | | | |
| No progression (SD, PR or CR) | 53 | 0.07 (0.03–0.11) | 0.03 (0.00–0.07) | 0.003 |
| Progression (PD) | 23 | 0.16 (0.07–0.20) | 0.14 (0.07–0.22) | 0.99 |
| *p*-Value (progression versus not) | | 0.001 | $<10^{-4}$ | |
| *RECIST status at week 24* | | | | |
| No progression (SD, PR or CR) | 22 | 0.04 (0.02–0.11) | 0.01 (−0.04–0.04) | 0.03 |
| Progression (PD) | 54 | 0.09 (0.06–0.16) | 0.08 (0.02–0.14) | 0.26 |
| *p*-Value (progression versus not) | | 0.008 | 0.0001 | |

SD: Stable disease; PR: Partial response; PD: Progressive disease.

**Table 3 – Distribution of the 76 patients according to RECIST status and to the variation in the GR between the pretreatment and the experimental period.**

| | Decreased GR | Increased GR | *p*-Value |
|---|---|---|---|
| *RECIST status at week 12* | | | |
| Non-progressive disease at week 12 (SD, PR or CR) | 33 | 20 | 0.45 |
| Progressive disease at week 12 (PD) | 12 | 11 | |
| *RECIST status at week 24* | | | |
| Non-progressive disease at week 24 (SD, PR or CR) | 15 | 7 | 0.44 |
| Progressive disease at week 24 (PD) | 30 | 24 | |

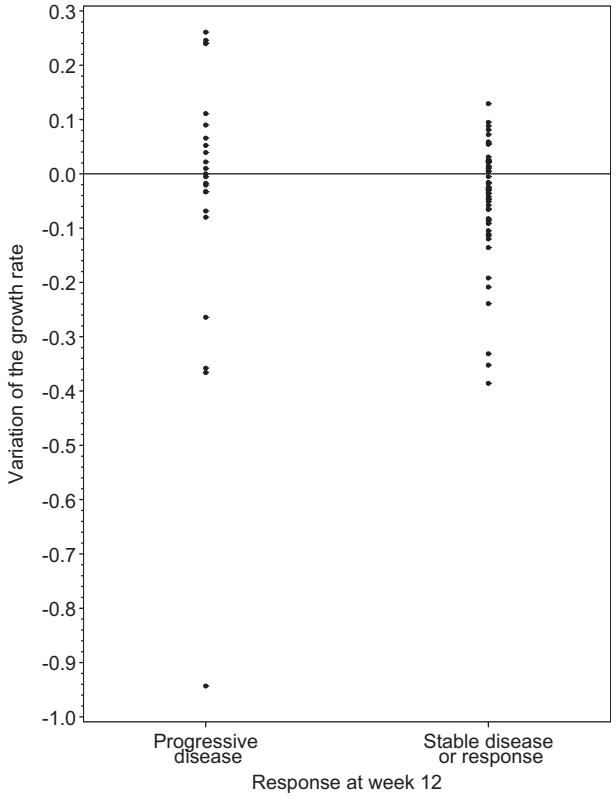


**Fig. 1 – Distribution of the difference between experimental and pre-treatment growth rate according to the RECIST response evaluation. A negative difference corresponds to a decreased growth rate (slowing down of tumour growth); a positive difference corresponds to an increased growth rate (tumour growth acceleration).**

pre-treatment period (Fig. 1). At week 24, 7 patients had an increased GR during the experimental period compared to pre-treatment out of the 22 patients classified as non-progressive according to RECIST and 30 patients had a decreased GR among the 54 classified in progression.

## 4. Discussion

This study aimed at evaluating the feasibility and usefulness of measuring the tumour growth rate during the pre-treatment and experimental period in order to better apprehend treatment efficacy.

As expected, the growth rate measured during the experimental period was significantly correlated with the evaluation of response according to the RECIST criteria. Patients classified with the higher growth rates were those classified as exhibiting progression according to RECIST. This finding mainly reflects the fact that the time needed to increase the tumour volume by 20%, and thus to characterise progression, is inversely related to the growth rate. In this respect, the evaluation of the growth rate during the experimental treatment period can be viewed as a quantitative measure of what is called tumour response in the RECIST system. The main difference concerns the occurrence of new lesions which is not taken into account for GR evaluation and is synonymous with progression in the RECIST system, which occurred in five patients in our series.

Our analysis of pre-treatment tumour growth showed two unexpected findings: the strong relation between RECIST evaluation of tumour response and pre-treatment growth rate and the lack of relation between RECIST and the variation of tumour growth rate between the pre-treatment and the experimental period.

Tumour growth rate measured during the pre-treatment period was significantly correlated with RECIST evaluations of response ($p < 0.01$). This observation means that either the pre-treatment growth rate is predictive of the tumour response that will be observed according to RECIST criteria and/or that the RECIST evaluation of tumour response is related to the natural history of tumours treated with poorly active compounds. Selection of patients harbouring indolent diseases is an approach well known by phase I trialists aiming at increasing the rate of patients with stable disease at first CT-scan evaluation. On the contrary fast growing tumours are typically not favored, notably at the initial dose levels of phase I trials.

The absence of a significant correlation between tumour response according to RECIST (at 12 or 24 weeks) and the variation in the GR between the pre-treatment and the experimental period suggest that what is named as evaluation of tumour response according to RECIST criteria is only partly related to the impact of treatment on tumour growth. Taken together, these 2 unexpected findings indicate the inadequacy of the RECIST system for evaluating treatment efficacy and mean that the evaluation of tumour response should take into account pre-treatment tumour growth measurements.

This study was performed on a phase I patient population. The main objective of phase I trials is to define the recommended dose for phase 2 trials. In theory, evaluating tumour response is only a secondary objective. Nevertheless, many go/no-go decisions regarding the fate of experimental compounds are also based on efficacy data resulting from phase I trials. The problem is more prominent in phase 2 trials, where response evaluation is often a critical end-point because response, usually used in an aggregate form such as a proportion of responders, is a key parameter for continuing or not a new experimental treatment. Our results suggest that performing a clinical trial on tumours with a small pre-treatment GR (slow growing tumours) might substantially increase the chance to conclude that an inactive treatment is efficient; conversely the evaluation of an active new treatment on patients with fast growing tumours (tumours with a high pretreatment GR) might unduly lead to stop the drug development.

Evaluating tumour growth rate changes may substantially improve the decision-making process regarding the assessment of efficacy in drug development. The ability to distinguish therapeutically induced ‘stable diseases’ from ‘false’ SD (ie indolent tumours enrolled in the trial) may be one of the key-benefits of GR evaluation. We are entering the era of personalised medicine; it might be useful to redefine response to treatment and identify patients in whom a treatment has a beneficial impact on tumour growth. The identification of patients with no decrease in the tumour GR

could help identify patients who may benefit from early treatment discontinuation, thus avoiding unnecessary toxicities and allowing early evaluation of better treatment options.

Our approach is feasible since most patients included in phase I/II trials have readily available pretreatment CT-scans. Pretreatment tumour growth assessment is thus mainly limited by the availability of the radiologist's time and could be easily implemented in centres with a motivated radiology service. The limitations of this strategy are those of the RECIST criteria which are widely accepted and used in clinical trials.[2–4]

## 5. Conclusion

Pre-treatment growth dynamics adds to the RECIST evaluation of tumour response and thus should be carefully documented. Patients with slow growing tumours are likely to be classified as disease control; even if the treatment has a minimal effect. Conversely, evaluation of an active new treatment on patients with fast growing tumours might unduly lead to early termination of a promising compound. The evaluation of response to experimental therapies or to recognised therapies should take into account the pre-treatment tumour growth. The current strategy presently advocated should be further tested in larger series.

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## Conflict of interest statement

None declared.

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